D.

Translation

09/913467

PATENT COOPERATION TREA[redacted]

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 10

Applicant's or agent's file reference PCT1126-019	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/00637	International filing date (*day/month/year*) 27 January 2000 (27.01.00)	Priority date (*day/month/year*) 13 February 1999 (13.02.99)
International Patent Classification (IPC) or national classification and IPC C12N 15/12		
Applicant OSTEOGENETICS GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31 August 2000 (31.08.00)	01 June 2001 (01.06.2001)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

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tional application No.
PCT/EP00/00637

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-32, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-26, filed with the letter of _____,
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1-10, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

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I. **Basis of the report**

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

Claims 1-26 filed with the letter of 29 June 2000 form the basis of the report. The claims meet the requirements of PCT Article 34(2)(b)).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box III.

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability.

As stated in the international search report, a search was carried out on the subject matter of Claims 3 and 13 (now Claims 3 and 10) insofar as they are supported by the description. In the opinion of the IPEA, this support is provided by Examples 1 and 2, that is a BMP-2 variant with SEQ. ID. NO. 3 inserted between amino acids 8 (Gln) and 9 (Arg) of a human Met-Ala-BMP-2, or a BMP-2 variant with SEQ. ID. NO. 4 inserted between amino acids 8 (Gln) and 9 (Arg) of a human BMP-2. Other specific embodiments that fall under the scope of Claims 3 and 10 cannot be taken from these examples.

This means that the international preliminary examination can relate to Claims 3 and 10 with the proviso that the "polypeptide" (see Claim 1) is a Met-Ala-BMP-2 or a BMP-2 and the insertion takes place between amino acids 8 and 9.

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	3 in part, 10 in part	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	3 in part, 10 in part	NO
Industrial applicability (IA)	Claims	3 in part, 10 in part	YES
	Claims		NO

2. Citations and explanations

The following documents were used for the purposes of the international preliminary examination:

D1: RUPPERT R. ET AL.: 'Human bone morphogenetic protein 2 contains a heparin-binding site which modifies its biological activity' EUR. J. BIOCHEM., Vol. 237, 1996, pages 295-302, XP000891887, cited in the application

D2: WO-A-97/47312 (COMMW BIOTECHNOLOGIES INC) 18 December 1997 (1997-12-18)

D3: FROMM J.R. ET AL.: 'Differences in the interaction of heparin with arginine and lysine and the importance of thee basic amino acids in the binding of heparin to acidic fibroblast growth factor.' ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, Vol. 323, No. 2, 10 November 1995 (1995-11-10), pages 279-287, XP000891918

D4: ALBERDI E. ET AL.: 'Pigment epithelium-derived factor (PEDF) binds to glycosaminoglycans: analysis of the binding site' BIOCHEMISTRY, Vol. 37, 1998, pages 10643-10652, XP002135602

D5: EP-A-0 414 915 (SUNTORY LTD; INOUE MASAYASU (JP)) 6 March 1991 (1991-03-06).

The cited prior art:

D1 describes a heparin-binding site in the N-terminal region of hBMP-2. It also describes an hBMP-2 variant that does not bind to heparin, yet has an increased specific activity (see D1, Introduction, last paragraph; Discussion, the last three paragraphs).

D2 describes synthetic heparin antagonists that do not use the heparin-binding sequence of the present application (SEQ. ID. NOs. 3 and 4) and which are used to treat cardiovascular illnesses (see D2, page 6, lines 1-11, and Claims 1-21).

D3 discusses the significance of arginine and lysine in the binding of heparin to aFGF. The binding domains mentioned therein also differ from SEQ.ID. NOs. 3 and 4 of the present application (see D3, abstract and Table 1).

D4 discusses the PEDF heparin-binding site. The binding domains mentioned therein also differ from SEQ. ID. NOs. 3 and 4 of the present application (see D4, abstract and Figure 8).

D5 describes an SOD with an additional heparin-binding site. The binding domains mentioned therein also differ from SEQ. ID. NOs. 3 and 4 of the present application (see D5, Claims 1-3).

Novelty and inventive step (PCT Article 33(2) and (3)):

The subject matter of Claims 3 and 10 (insofar as examined) is novel. D1 can be considered the

closest prior art for the purposes of inventive step. As already stated, D1 discusses the role of heparin in the activity of hBMP-2 (see discussion), but does not lead to the conclusion that the introduction of an additional heparin-binding site would result in an increase in biological activity. An inventive step can therefore be acknowledged for the aforementioned subject matter.